REMARKS

Upon entry of the present amendment, claims 1 to 10, 14, 15, 23 to 27, 40, 43 to 51, and 84 to 91 will be pending.

No new matter is added with the amendments and newly added claims. The amendment to claims 1 and 40 indicating that the method is for detecting liver cancer is supported for example by page 6, line 30 to page 7, line 1. The amendment to claims 1, 4, 27, and 40 indicating that the method detects hypermethylation of a promoter region at approximately nucleotide positions -539 to -239 of the GSTP1 gene is supported for example, by page 12, lines 15-22, Example 3 and claim 79 as originally filed.

The amendment to claims 1, 3, 4, 27, and 40 indicating that the method detects hypermethylation of a promoter region at approximately nucleotide positions -195 to +35 of the GSTP1 gene is supported by page 44, lines 19 to 23. The amendment to claim 1 indicating that the sample is from hepatic tissue, bile, or blood is supported by claims 12 and 13 as originally filed.

The amendment to claim 14 is supported for example, by page 18, lines 15-18 and page 19, lines 3-7. The amendments to claims 2, 6, 7 and 23 correct minor typographical or grammatical errors. As such, the amendments do not add new matter.

Newly added claims 86 and 87 are supported for example, by page 7, lines 1 to 8. Newly added claims 88 and 89 are supported for example, by page 44, lines 24-25. Newly added claims 90 and 91 are supported for example, by Example 3. As such, the newly added claims do not add new matter.

The amendments and newly added claims do not require a new search or raise new issues for consideration because they are directed to issues already raised by the Examiner or define Applicant's invention more clearly. It is submitted that the amendments place the claims in condition for allowance or in better condition for appeal by reducing the number of issues for consideration on appeal. The amendments were not made earlier in the prosecution because it is maintained that the previously pending claims are allowable. Since the amendments do not add new matter or require a new search or consideration, and place the claims in condition for

allowance or in better condition for appeal, and since a greater number of finally rejected claims have been cancelled than new claims added, entry of the amendments is respectfully requested. Applicants respectfully request reconsideration of the present application in view of the amendments and the following remarks.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Applicants respectfully traverse the rejection of claims 14-15 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action alleges that claim 14 is indefinite in allegedly being unclear as to where in the method of claim 6 the step recited in claim 14 is carried out.

Claim 14 has been amended to depend from claim 1, thus clarifying that the detecting step of claim 14 comprises contacting nucleic acids in the sample, or a GSTP1 amplification product thereof, with a methylation sensitive restriction endonuclease. As such, it is submitted that amended claim 14 clearly defines the steps required to practice the claimed method and, therefore, respectfully requested that the rejection under 35 U.S.C. § 112, second paragraph, be removed.

Rejection Under 35 U.S.C. 112, First Paragraph

Applicants respectfully traverse the rejection of claims 1-51, 84, and 85 under 35 U.S.C. § 112, first paragraph. The Office Action alleges that the specification does not teach one skilled in the art how to make and/or use the invention commensurate in scope with the claims. The Office Action reiterates the arguments of the previous Office Action in support of the rejection and provides responses to Applicants' arguments included in the Response filed on October 29, 2002, as set forth below.

As a preliminary matter, the rejection is moot with respect to claims 28-39, 41, and 42 because these claims are canceled herein. Furthermore, with respect to the ground for rejection related to detecting changes in expression of GST, claims 28-39 have been canceled herein to

advance prosecution of the pending application. As such, the pending claims do not encompass detecting liver cancer by comparing GST levels. Rather, the pending claims are directed to detecting a liver cancer by detecting hypermethylation of a promoter region at approximately nucleotide positions -539 to -239 or -195 to +35 of a GSTP1 gene transcription start site. Therefore, it is respectfully submitted that the rejections based on detecting GSTP1 expression levels is moot.

The Office Action acknowledges that the specification is "enabling for a method of detecting hepatocellular carcinoma (HCC) or liver cancer" (Office Action page 4, first full paragraph), but alleges that the specification does not enable detecting a hepatic cell proliferative disorder because only analysis of hepatocellular carcinoma, and no other type of cell proliferative disorder, is exemplified. Although Applicants maintain that the specification enables detecting a hepatic cell proliferative disorder using the disclosed methods, the claims nevertheless have been amended to such that a liver cancer (claims 1-10, 14-15, 23-27, 40, 43-51, 84-85, and 88-91), including hepatocellular carcinoma (claims 86 and 87), is detected. Accordingly, in view of the acknowledgement in the Office Action that detecting HCC or liver cancer is enabled, it is respectfully requested that this ground for rejection be removed.

The Office Action further alleges that the specification does not provide guidance or working examples illustrating that *any* hyperproliferative disorder can be detected by detecting a *methylated* CpG containing glutathione s-transferase gene (GST). Furthermore, the Office Action asserts that Herman et al. teach that human genes are known to be methylated and that hypermethylation of GSTP1 is associated with neoplastic tissue. Therefore, it is alleged that the skilled artisan would not be able to detect a hepatic cell proliferative disorder based solely on the detection of methylated CpG containing GST nucleic acid. The present claims clarify that liver cancer is detected by detecting *hypermethylation* of the recited promoter regions. Therefore, it is respectfully submitted that this ground for rejection be removed.

Regarding sample type, the Office Action acknowledges that the specification enables a method wherein the sample is hepatic tissue, bile, or blood (Office Action, page 4, first full paragraph), but alleges that the specification does not provide guidance to support that a sample

from any source could be used, such as, for example, colon or lymphatic tissue, or that the source could be any biological fluid, such as ejaculate or urine. It is further alleged that the specification provides no evidence, for example, that a colon sample could be used to detect hepatic cell proliferative disorder, or that in an ejaculate sample, hypermethylation of a GST gene would be indicative of liver cancer rather than prostate cancer. Although the Applicants maintain, for reasons of record, that the specification would have enabled the skilled artisan to use any of various samples to detect a hepatic cell proliferative disorder according to the disclosed methods, in order to advance prosecution of the present application, the claims as amended recite that the sample is a "hepatic tissue specimen, bile, or blood." Accordingly, in view of the acknowledgement in the Office Action that detecting HCC or liver cancer in the recited samples is enabled, it is respectfully requested that this ground for rejection be removed.

The Office Action maintains that the specification does not enable the claimed invention because allegedly it does not establish an association between a hepatic cell proliferative disorder and detection of a methylated CpG containing GST nucleic acid in *any subject*, for example, a rat. Although the Applicants traverse the rejection for reasons of record, to advance prosecution of the pending application, claims 1 and 40, from which the remaining claims depend, have been amended to recite that the methods are for detecting liver cancer *in a human*. As such, it is submitted that this ground for rejection is moot.

It is further alleged that the specification does not teach an association between hepatocellular carcinoma and hypermethylation *in any region* of a GST nucleic acid. The claims have been amended to more clearly indicate that a method of detecting liver cancer is practiced by detecting hypermethylation of the promoter region at approximately nucleotide positions -539 to -239 or -195 to +35 of a GSTP1 gene transcription start site. Applicants point out that hypermethylation of such regions is supported, for example, by Example 3 of the application, which demonstrates that hypermethylation of the promoter region at approximately nucleotide positions -539 to -239 of the GSTP1 gene is indicative of liver cancer, and Example 5, which demonstrates that hypermethylation of the promoter region at approximately nucleotide positions

-195 to +35 of the GSTP1 gene is indicative of liver cancer. Accordingly, it is respectfully submitted that this ground for rejection be removed.

The Office Action also alleges that the specification does not teach the detection of HCV, and does not provide any guidance or working examples that detecting HBV or HCV and detecting a methylated CpG containing GST nucleic acid is indicative of a hepatic cell proliferative disorder. The Office Action asserts that since a CpG containing GSTP1 nucleic acid is inherently methylated, the detection of HBV along with methylated GSTP1 could be indicative of hepatitis B infection rather than a hepatic cell proliferative disorder.

Applicants point out that claims 26 and 50 refer to further detecting HBV or HCV, and that Example 4 of the specification sets out methods and results related to both the detection of HBV and HCV and the correlation of this detection with hepatocellular carcinoma. As indicated in Table II of Example 4 (page 42), exposure to HBV and/or HCV can be detected, for example, by detecting HBV surface antigen or by detecting antibodies against these viruses, as is well known in the art. Furthermore, the results presented in Example 4 and Table II demonstrate that individuals who suffer from liver cancer often have been exposed to HCV or HBV. In fact, of the 28 hepatocellular carcinoma cases studied, only 1 case did not show an infection with HBV and/or HCV (see page 41, lines 1-5). Therefore, the detection of HCV or HBV can be used to increase the confidence that detecting hypermethylation of the promoter region at approximately nucleotide positions -539 to -239 or -195 to +35 of a glutathione-S-transferase GSTP1 gene transcription start site in a human subject is indicative of liver cancer. Thus, it is submitted that the specification clearly establishes that the further presence of HBV or HCV with hypermethylation of a CpG-containing promoter region of the GSTP1 gene is indicative of liver cancer. Accordingly, it is respectfully submitted that this ground for rejection be removed.

For the reasons set forth above, it is submitted that the pending claims are fully enabled by the present specification such that one skilled in the art would have known how to practice the claimed methods without undue experimentation. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, first paragraph, be removed.

In view of the amendments and the above remarks, it is submitted that the application is in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50 1355

Respectfully submitted,

Date: May 12, 2003

Lisa A. Haile, Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
CUSTOMER NUMBER 28213